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IN THE

Supreme Court of the United States

OCTOBER TERM, 1988

G & W LABORATORIES, INC.,
Petitioner,

v.

UNITED STATES OF AMERICA,
Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Third Circuit

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PETITIONER'S REPLY BRIEF

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PETITIONER'S REPLY BRIEF

Petitioner G & W Laboratories, Inc. (G & W) submits this brief in reply to the brief of the Government in opposition to G & W's petition for a writ of certiorari. The brief addresses issues newly raised in the Government brief.

ARGUMENT

1. The Government brief fails to respond to G & W's arguments that in the courts below there was erroneous deference in reliance on *Chevron U.S.A. Inc. v. National Resources Defense Council*, 467 U.S. 837 (1984) to litigating positions taken by FDA which are inconsistent

with other administrative actions which FDA took prior to this case and also with a recently promulgated FDA Notice of Proposed Rulemaking.

The only partial response on this question comes at the end of footnote 8, citing the *Morton* and *Gardebring* cases for the proposition that an agency's position is not necessarily to be disregarded because the agency first took the position in response to the litigation in question. While this may be true, neither case addresses a situation in which the agency's litigating position is directly contradictory to other agency decisions, taken both before and after the litigation. Both *Morton* and *Gardebring* involve situations in which the agency wrote on a clean slate, not one in which its litigating position is inconsistent with other agency actions. Here the agency is contending that, as a matter of law, studies with one product cannot support the effectiveness of another unless there is actual bioequivalence data available to show equivalence between the two products. That is a factual question which the FDA has in fact decided differently in other contexts, see petition, pp. 10-16.

G & W points out in its petition (pp. 12-16) that the FDA took actions in its 1988 Notice of Proposed Rulemaking on Anorectal Drug Products which demonstrate that the deference to FDA's position below was improper. On pages 10-11 of its brief, the Government argues that the 1988 Notice does not apply to Anucort for various reasons and should not be relied upon by the Court.

G & W never suggested that the 1988 Notice applies directly to Anucort. It only pointed out that the Notice contained a number of FDA statements on scientific and legal positions which are contrary to the agency positions asserted in this case to which the courts below gave deference under the *Chevron* doctrine. In any event, it should be noted that in footnote 8, the Government brief refers to the same 1988 notice as "the 1988 Federal

Register Notice on products like Anucort" and also relies on the Notice in footnote 6, at the same time it argues, on page 12, that "the proposed rule does not apply to products like Anucort . . ." This selective, inconsistent application of authorities and principles is what has led to the complex legal arguments in this case.

Most significantly, however, whatever the Government's inconsistent positions as to the applicability of this Notice, the Notice clearly requires no bioequivalence data for any products (including suppositories) to support findings that they are "not new drugs." G & W agrees that this rule as applied in this Notice is also applicable to "products like Anucort."

2. G & W agrees with the Government that the *Hynson* case requires that there be adequate and well-controlled clinical studies establishing safety and effectiveness of Anucort to support general recognition of effectiveness among exports, and that *Generix* requires that these studies and the general recognition be applicable to the actual product involved and not just to its active ingredients, see brief, pp. 5-6. Both of these requirements are met in this case.

The affidavits submitted by G & W's experts rely on adequate and well-controlled clinical studies which in their opinions establish the safety and effectiveness of the Anucort product. The Government has not questioned that these studies are adequate and well controlled as required by *Hynson*. The uncontroverted expert affidavits further attest that the products on which these studies were conducted were such that, as a matter of fact, the studies establish the effectiveness of Anucort. *Generix* requires no more. Whether actual clinical studies showing bioequivalence are required for Anucort is at most a factual issue which must be determined at trial.

The government also argues that, as a matter of law, a showing of bioequivalence is always required before

clinical studies of another product may be relied upon to support "general recognition" of effectiveness among experts, citing 21 U.S.C. (Supp. IV) 355(j)(2)(A)(iv) (hereafter subparagraph A(iv)). This provision, which was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, sets the standards for FDA to apply in approving abbreviated new drug applications (ANDAs) for generic copies of drugs already approved by FDA. It does not apply to determinations of whether drugs are generally recognized as safe and effective, and there are significant legal and factual problems raised by an attempt arbitrarily to apply subparagraph A(iv) to this different statutory determination.[1]

An ANDA approval is based specifically on the safety and effectiveness of a designated, previously approved drug and there is thus good reason to ensure by a bioequivalence requirement that the specific data supporting that drug applies to generic copies of it. A general recognition determination under 21 U.S.C. 321(p), on the other hand, does not necessarily rely on data relating to one drug but may, as in the case of Anucort, may be based on clinical studies of a number of related drugs from which experts can fairly and responsibly conclude that the drug is generally recognized as safe and effective. Whether a showing of bioequivalence is necessary for a study of another product to be relevant to this determination of general recognition is a factual question, and there is no policy reason requiring such studies in all cases if in fact it is not scientifically necessary.

The enactment of subparagraph A(iv) did not, as the Government contends, answer the question which this Court left open in *Generix*, i.e., whether the FDA must

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[1] 21 U.S.C. 321(p) defining "new drug" was not amended in 1984 to incorporate any such bioequivalence study requirements into the determination of whether a product is "generally recognized" as safe and effective among experts.

make a factual showing that there is a reasonable possibility that a drug is not bioequivalent before the courts will impose a bioequivalence requirement in a determination of "new drug" status under 21 U.S.C. 321(p).

3a. The Government is also factually incorrect in its description of the provisions of subparagrph A(iv). Specifically, footnote 4 of the Government brief inaccurately states that there is only one exception, "not applicable here," to the requirement for bioavailability studies, i.e., the substitution of one active ingredient in a drug product containing more than one active ingredient. The exception in subparagraph A(iv) in fact applies whenever a petition is approved under 21 U.S.C. (Supp. IV) 355(j)(2)(C) (hereafter subparagraph C). Subparagraph C applies not only to petitions to substitute one active ingredient for another, but also to petitions to allow different routes of administration, dosage forms and strengths. In this case, the studies relied upon by G & W's experts in support of Anucort involve in some cases, different (but related) active ingredients, different (but related) dosage forms (creams, ointments, etc., rather than suppositories) and in some cases different (but related) dosage strengths, all of which could be covered by an approved petition under subparagraph C.

Thus, even if subparagraph A(iv) were to be applied to a determination of whether a product is a "new drug" the portion of it which would be applicable here is not the requirement of a bioequivalence study, but the exception for applications covered by an approved subparagraph C petition. The exception would only require information to show that the "active ingredients . . . are of the same pharmacological or therapeutic class as" the drug to which it is being compared, and that "it can be expected to have the same therapeutic effect" as the drug when administered to patients for the same conditions of use. This is precisely the kind of information which was provided by G & W's experts in their affidavits. Whether

this information on Anucort meets the statutory standard would of course be an issue of fact to be determined at trial.

3b. An additional reason why the bioequivalence requirement of subparagraph A(iv) does not properly apply here is that Anucort comes within a category of drugs for which FDA has by regulation waived the *in vivo* bioequivalence requirement.

The Government argues (brief, p.10) that FDA's regulation which waives bioavailability for topical drugs does not apply to a suppository like Anucort because it now (for this litigation) defines a topical drug as one which is applied directly to the site at which it is to have its effect. Based on this newly made up definition, they argue that a rectal suppository is not top[illegible] because it is not applied directly to the site of its external hemorrhoid indication. There are, however, mechanisms by which a rectal suppository can be directly applied to external hemorrhoids. It can be ~~effective, for~~ example, because the suppository melts, seeps down the anal canal, and spreads to cover the external sites. There is no evidence in the record which would dispute this conclusion. The Government quotes in footnote 8 of its brief from a comment made by FDA in the preamble of its 1988 Notice of Proposed Rulemaking rejecting this mechanism of application of suppositories to external sites as ineffective. However, this is merely a tentative position taken by FDA in an ongoing rulemaking proceeding. It confirms that there is a factual dispute about the effectiveness of this "seepage" mechanism, but it is not a reasonable basis for considering this factual issue to be resolved, as a matter of law, against G & W in this case.

Finally, the Government also argues that since it cannot waive the statutory requirement for bioequivalence in approving ANDAs for products which are admittedly "new drugs," that requirement must apply in determin-

ing whether a product is a "new drug". Whether or not this is an accurate reading of the statutory provision, it does not resolve the question of what type of showing must be made to establish bioequivalence. Indeed, despite this alleged inability to waive the requirement, FDA routinely waives any requirement for *in vivo* testing, accepting instead evidence as to formulation and compliance with good manufacturing practices. (See brief, fn. 6) No allegation has ever been made that Anucort fails to meet proper formulation or good manufacturing practice requirements. Moreover, any such question would again raise factual issues which would have to be resolved at trial.

CONCLUSION

This case involves significant questions as to the application of *Chevron* in cases in which the Government's litigating position is inconsistent with prior and subsequent agency actions, and presents important federal questions applicable to many existing products as to the data and information necessary to establish that a drug product is "generally recognized as safe and effective among experts." This petition for certiorari should therefore be granted.

Respectfully submitted,

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